JC07 Rec'd PCT/PTO 07 FEB 2002

FORM PTO-1390 (Modified) (REV 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **PJ3732USW**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR: 10/049167

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/05200	**August 3, 2000**	**August 7, 1999**

TITLE OF INVENTION

AQUEOUS NASAL FORMULATION

APPLICANT(S) FOR DO/EO/US

AKUTSU, Rika, HOSOYA, Kenji, KAWAMURA, Koho, MISHIMA, Yahuhiro , NOZAKI, Tomohisa and SUGIBAYASHI, Nobuya

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include itens (5), (6), (9) and (24) indicated below.
4. ☐ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   - a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   - b. ☒ has been communicated by the International Bureau.
   - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   - a. ☐ is attached hereto.
   - b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   - a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   - b. ☐ have been communicated by the International Bureau.
   - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. ☐ An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☒ A copy of the International Search Report (PCT/ISA/210).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 - 1.825.
20. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
21. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
22. ☒ Certificate of Mailing by Express Mail
23. ☒ Other items or information:

    Copy of PCT Cover Sheet

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
10/049162	PCT/JP00/05200	PJ3732USW

24. The following fees are submitted:	CALCULATIONS PTO USE ONLY
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :	
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1040.00**	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$890.00**	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$740.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$710.00**	
☐ International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**	
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	9 - 20 =	0	x $18.00	**$0.00**
Independent claims	1 - 3 =	0	x $84.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**
TOTAL OF ABOVE CALCULATIONS			=	**$890.00**
☐ Applicant claims small entity status. See 37 CFR 1.27). The fees indicated above are reduced by 1/2.				**$0.00**
SUBTOTAL			=	**$890.00**
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	**$0.00**
TOTAL NATIONAL FEE			=	**$890.00**
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐				**$0.00**
TOTAL FEES ENCLOSED			=	**$890.00**
				Amount to be: refunded $
				charged $

a. ☐ A check in the amount of _____ to cover the above fees is enclosed.

b. ☒ Please charge my Deposit Account No. **07-1392** in the amount of **$890.00** to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **07-1392** A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

23347
PATENT TRADEMARK OFFICE

SIGNATURE

James P. Riek
NAME

39,009
REGISTRATION NUMBER

7 Feb 2002
DATE

Express Mail Label No.:
EL395941438US

IN THE UNITED STATES PATENT OFFICE

Applicant	:	AKUTSU, et al.
Appl. No.	:	not yet assigned
Filed:	:	herewith
Grp./A.U.	:	not yet assigned
Examiner	:	not yet assigned
Docket No.	:	PJ3732USW

Honorable Commissioner of Patents
Washington DC 20231

PRELIMINARY AMENDMENT

Sir:

Please amend the above-identified application as follows:

In the Abstract

Please substitute the attached Abstract, which has been placed on a separate sheet of paper according to US practice, as required under 37 CFR 1.72(b).

In the Specification

On the first line of the specification, after the Title, please add

--This application is filed pursuant to 35 U.S.C. §371 as a United States National Phase Application of International Application No. PCT/ JP00/05200 filed 3 August, 2000, which claims priority from GB 9918559.7 filed 7 August 1999 in the United Kingdom.--

REMARKS

Applicants have attached an abstract on a separate sheet of paper as required by US practice. Applicants have amended the specification for purposes of adding the priority

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information. It is respectfully submitted that the present application is in condition for allowance. An early consideration and notice of allowance are earnestly solicited.

Respectfully submitted,

Date:
29 Jan 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

On the first line of the specification, after the Title, the following text was added

--This application is filed pursuant to 35 U.S.C. §371 as a United States National Phase Application of International Application No. PCT/ JP00/05200 filed 3 August, 2000, which claims priority from GB 9918559.7 filed 7 August 1999 in the United Kingdom.--

AQUEOUS NASAL FORMULATION

ABSTRACT

An aqueous nasal formulation comprising beclomethasone dipropionate anhydrate for use in the treatment of respiratory disorders.

10/049167

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DESCRIPTION

AQUEOUS NASAL FORMULATION

The present invention relates to an aqueous nasal formulation for use in the treatment of respiratory disorders.

Aerosol formulations are commonly used as effective anti-inflammatory treatments, but have implications with environmental safety. The most commonly used propellants in such formulations were previously chlorofluorocarbon containing (or CFC) propellants, however, these are currently being phased out, following the 1987 Montreal Protocol Agreement.

Since then, safer hydrogen containing fluorocarbons have been used as propellants in aerosol formulations, but these are relatively expensive and the environmental impact of these new propellants has also been questioned.

Thus, there is a need for safe anti-inflammatory treatments such as aqueous nasal formulations. The corticosteroid beclomethasone dipropionate (9α-chloro-16β-methyl-1,4-pregnadiene-11β, 17α, 21-triol-3, 20-dione-17, α21-dipropionate) is well known as a topical anti-inflammatory steroid and is found in aqueous nasal formulations.

Prior aqueous nasal formulations containing beclomethasone dipropionate, used in treating such indications as allergic rhinitis (such as Beconase™ AQ) have utilised beclomethasone dipropionate monohydrate in addition to the following constituents:

Anhydrous dextrose;
Avicel RC591 (Microcrystalline cellulose and carboxymethylcellulose sodium);
Phenylethyl alcohol;
Benzalkonium chloride;

Polyoxyethylene (20) sorbitan monooleate;
and purified water

Beclomethasone dipropionate monohydrate is not currently licensed in all territories of the world (notably not in Japan) and as a consequence, nasal formulations containing such a medicament cannot be marketed in such territories without substantial research effort and expense. However, there is an alternative anhydrous form of beclomethasone dipropionate, previously used in a nasal formulation (eg. Aldecin™ AQ) which contains the following constituents:

Micronised beclomethasone dipropionate anhydrate;
Avicel RC591 (Microcrystalline cellulose and carboxymethylcellulose sodium);
Glycerol;
Propylene glycol;
Polyoxyethylene (20) sorbitan monooleate;
and purified water.

However, in the absence of a sealed pressurised container, as with the propellant based delivery systems, these formulations may be prone to contamination. As a consequence, potentially harmful bacteria may contaminate the formulation and then be inhaled directly into the nasal cavity. Additionally, these formulations have also been known to cause irritancy, which is especially undesirable in respect of paediatric treatment.

Thus, according to the present invention we provide a pharmaceutical formulation which comprises an aqueous solution of carboxy methylcellulose sodium, glycerol, propylene glycol and polyoxyethylene (20) sorbitan monooleate, containing suspended therein particulate microcrystalline cellulose

and beclomethasone dipropionate anhydrate characterised in that said aqueous suspension further comprises:

Dextrose;
Phenylethyl alcohol;
Benzalkonium chloride;
Disodium hydrogen orthophosphate; and
Citric acid

The presence of dextrose, disodium hydrogen orthophosphate and citric acid is intended to overcome the irritancy problems associated with current anhydrous beclomethasone dipropionate formulations. This improvement is believed to be mediated through the dextrose acting as an isotonicity adjusting agent. Furthermore, the beclomethasone dipropionate anhydrate may be stabilised by appropriate selection of pH using disodium hydrogen orthophosphate and citric acid to act as a buffer.

In addition, phenylethylalcohol and benzalkonium chloride are present within the formulation to act as preservatives.

Dextrose is preferably used as dextrose anhydrous. Disodium hydrogen orthophosphate is preferably used as disodium hydrogen orthophosphate anhydrous. Citric acid is preferably used as citric acid monohydrate. Microcrystalline cellulose and carboxy methylcellulose sodium is preferably used as the branded product Avicel RC591 (which typically contains 87-91% microcrystalline cellulose and 9 -13% carboxy methylcellulose sodium).

Particulate beclomethasone dipropionate anhydrate will suitably be micronised and have a mean particle size less than 20μm, preferably less than 10μm, especially 1-5μm.

Particulate microcrystalline cellulose will preferably have a particle size in the range 1 to 100μm.

A pharmaceutically acceptable amount of micronised beclomethasone dipropionate anhydrate is present within the formulation, which is preferably between 0.025-0.25% (w/w), especially 0.1% (w/w). The branded product Avicel RC591 and propylene glycol are suspending agents and are desirably added in a suitable amount to achieve this function, preferably between 1-5% and 0.1-20% (w/w) respectively, especially 1.5% and 1.0% (w/w) respectively.

We believe that Avicel RC591 acts as a suspending agent by imparting thixotropic properties to the formulation, wherein the formulation may become a stable suspension upon being stirred, shaken or otherwise disturbed. We similarly believe that propylene glycol aids stabilisation of the formulation by reducing the bubbles which arise due to the presence of Avicel RC591 and benzalkonium chloride in the formulation.

Glycerol is added in a suitable amount to achieve its desired function as an excipient which reduces the solubility of beclomethasone dipropionate anhydrate in formulation; preferably the amount of glycerol will be such as to make the beclomethasone dipropionate anhydrate essentially insoluble in the formulation. An amount of glycerol which is preferably between 0.1-6% (w/w), especially 4.0% (w/w) will be suitable. The wetting agent, polyoxyethylene (20) sorbitan monooleate (typically supplied as the branded product Polysorbate 80) is desirably added in a sufficient quantity to achieve this function, preferably between 0.001-0.01% (w/w), especially 0.007% (w/w). The components disodium hydrogen orthophosphate anhydrous and citric acid monohydrate, which act as buffers, are desirably added in a suitable amount to achieve a final pH, following adjustment if necessary, of between 5 and 6, especially 5.5. Suitable concentrations of each component are 0.01-0.4% and 0.01-0.2% (w/w)

respectively, especially 0.31% and 0.2% (w/w) respectively. Dextrose anhydrous is an isotonicity adjusting agent and is added in a suitable amount to achieve isotonicity with fluids of the nasal cavity. Suitable concentrations are between 0.1 and 5% (w/w), especially 5.0% w/w. Phenylethyl alcohol and benzalkonium chloride are preservatives which are preferably added in concentrations between 0.001-1% (v/w) and 0.001-1% (w/w) respectively, especially 0.275% (v/w) and 0.02% (w/w), respectively.

Besides its very good antiallergic properties and the above mentioned reduction in irritancy, the benefits of the invention may include the following:

Surprisingly, we have found that phenylethylalcohol has preservative properties by killing Pseudomonas cepacia (now known as Burkhoderia cepacia) by a synergistic effect with benzalkonium chloride. Ps. cepacia is a bacterium which is capable of opportunistic infections such as blood poisoning and due to the bacterium being largely resistant to antibiotics, clinical treatment is complex. Results demonstrating this effect are shown in Figure 7.

A formulation of the present invention may be prepared by the manufacturing process according to the flow diagram shown in Figure 1.

A typical container suitable for a formulation of the present invention may be of the type exemplified in Figures 2 and 3. As a further aspect of the present invention we provide a container comprising a pharmaceutical formulation according to the present invention suitable for delivering it in the form of a nasal spray.

A suitable dosing regime for the formulation of the present invention would be for the patient to inhale deeply subsequent to the nasal cavity being cleared. During inhalation the formulation would be applied to one nostril while the other is

manually compressed. This procedure would then be repeated for the other nostril.

Wherein the patient is adult, two inhalations would be administered by the above procedure (100μg beclomethasone dipropionate anhydrate in total) four times each day.

Wherein the patient is a child, two inhalations would be administered by the above procedure (100μg beclomethasone dipropionate anhydrate in total) two times each day.

It will be appreciated that the above dosing regime should be adjusted according to the patient's age, body weight and/or symptom severity. However, the maximum daily dose should not exceed 16 inhalations for an adult and 8 inhalations for a child. If remission of the nasal symptoms is observed, the dose should be decreased as appropriate.

Examples of disease states in which the formulation of the present invention has potentially beneficial anti-inflammatory effects include allergies associated with the nasal cavity, more particularly allergic rhinitis.

Thus, according to a further aspect of the invention we provide a pharmaceutical formulation of the present invention for use in the treatment or prophylaxis of allergic rhinitis.

We also provide a use of a pharmaceutical formulation of the present invention in the manufacture of a medicament for the treatment or prophylaxis of allergic rhinitis.

More specifically, the formulation of the present invention may be illustrated by reference to the following example:

Example 1

A solution of propylene glycol (0.3kg) in purified water (23.6kg) is dispersed by mixing at 2000rpm for 5 mins. To this solution, dextrose anhydrate (1.5kg), phenylethyl alcohol (82.5g) and microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC591; 0.45kg) is then added separately and mixed for a further 10, 5 and 30 mins, respectively. The dispersing is then ceased and the mixture is allowed to stand for 60 mins to hydrate. Dispersion is resumed at 3000rpm for 10 mins and then re-adjusted to 2000rpm.

Anhydrous disodium hydrogen orthophosphate (93g) is added to purified water (1.8kg) and dissolved by mixing at 3000rpm for 15 mins. This solution is then mixed into the dispersing suspension for 5 mins as is a solution of citric acid, prepared by manually mixing citric acid (0.06kg) with purified water (600g).

Glycerol (1.2kg) was heated at 48°C ± 2°C and polyoxyethylene (20) sorbitan monooleate (Polysorbate 80; 2.1g) is then dissolved in the glycerol. A slurry is then formed by mixing micronised beclomethasone dipropionate anhydrate (30g) with the glycerol and polyoxyethylene (20) sorbitan monooleate solution at 4500rpm at 48°C ± 2°C for 30 mins. This slurry is then added to the dispersing suspension and mixed for 15 mins.

A solution of benzalkonium chloride (50% w/v; 11.82g) is then diluted with purified water (220g), heated to 35-40°C and then mixed with the drug suspension for 3 mins. Dispersion is then ceased, pH is adjusted to that of an optimum value, typically between 5 and 6, especially 5.5. The drug suspension is then filtered through 100 mesh filters and stored prior to filling into clean

bottles. This procedure results in the components being present in the following concentrations:

Micronised beclomethasone dipropionate anhydrate	0.1% (w/w)
Dextrose anhydrous	5.0% (w/w)
Microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC591)	1.5% (w/w)
Phenylethyl alcohol	0.275% (v/w)
Benzalkonium chloride solution 50% (w/v)	0.04% (v/w)
Glycerol	4.0% (w/w)
Propylene glycol	1.0% (w/w)
Polyoxyethylene (20) sorbitan monooleate	0.007% (w/w)
Disodium hydrogen orthophosphate anhydrous	0.31% (w/w)
Citric acid monohydrate	0.2% (w/w)
Purified water	to 100%.

Biological Data

The formulation of the present invention, Example 1 (beclomethasone dipropionate anhydrate aqueous nasal spray, hereinafter defined as BANS) which delivers 50 μg BDP in a single spray was tested in a variety of assays to deduce its effect upon nasal symptoms when compared with controls and a prior art formulation (Aldecin™ AQ).

1) Effect of BANS on TDI-induced nasal symptoms in sensitised guinea pigs.

Guinea pigs were immunised by 2 x 5 days intranasal application of 10% TDI (toluene 2, 4-diisocyanate) at intervals of 3 weeks. One or two weeks after the final sensitisation, a nasal allergy like response (sneeze, rhinorrhea, nasal obstruction) was provoked by intranasal application of 5% TDI. Drugs were

topically applied 0.5, 1 or 4 hr before the provocation (1 spray each nostril equivalent to 100 μg BDP), however, a control utilised animals sensitised with 5% TDI without drug treatment. Any nasal symptoms were then observed (eg. sneezing, rhinorrhea and nasal obstruction) and scored according to the criteria displayed in Table 1.

Table 1: Criteria used to assign a nasal symptom score for each group

Symptom	Score			
	0	1	2	3
Sneezing	Not observed	1-4	5-11	>12
Watery rhinorrhea	Dry nostril	Snivel observed, but remains within nostril	Snivel leaks from nostril and wets the nasolabial portion, but does not discharge	Snivel drops from the nose
Nasal obstruction	Not observed	Observed	-	-

The sum of the score was regarded as the nasal response of the animal and a 'mean score' value was given for the mean of the scores of each group. The results of this investigation are shown in Figure 4.

2) Effect of BANS on antigen induced nasal vascular permeability in sensitised rats.

Rats were immunised with DNP-As and the animals with 72 hr –PCA titre over x50 were used. Under the anaesthesia, the nasal cavity of the rat was perfused with saline. After the dye (4% pontamine sky blue (Brilliant blue) 5 ml/kg) was intravenously injected, the perfusate was collected for 10 min. Thereafter, the

antigen solution was perfused for 10 min followed by perfusion with saline for further 30 min. The dye concentration of the perfusate collected was determined by absorbance at 616nm. Drugs were topically applied 24hr and 1hr before the provocation (2 sprays at each time equivalent to 100μg BDP). Controls were prepared which utilised antigen challenged sensitised animals without drug treatment (control) and BANS placebo treatment (vehicle). The results of this investigation are shown in Figure 5.

3) Effect of BANS on the increase in intranasal pressure after antigen challenge in sensitised guinea pigs.

Guinea pigs were immunised with OVA by subcutaneous administration in mixture with FCA. The animals with 4 hr-PCA titre over x50 were used. Under the anaesthesia, a Y-shaped cannula was inserted into the trachea of larynx side. One end of the cannula was connected to the transducer to measure intranasal pressure and the other end to air bomb to supply contact flow of the air. After instillation of the antigen solution into the nose, intranasal pressure was measured for 28 min. Drugs were topically applied 24 hr and 1 hr before the provocation (4 sprays at each time equivalent to 200 μg BDP). Controls were prepared which utilised antigen challenged sensitised animals without drug treatment (control) and BANS placebo treatment (vehicle). The results of this investigation are shown in Figure 6.

4) Challenge test of BANS against Ps. Cepacia

Formulations corresponding to BANS and the same formulation containing only 0.02% (w/w) benzalkonium chloride as preservative (i.e. no phenylethyl alcohol) and the same formulation containing only 0.275% (v/w) phenylethylalcohol as preservative (i.e. no benzalkonium chloride) were challenged with an innoculum of Ps cepacia. The results, shown in Figure 7, demonstrate that the combined

preservative is much improved in respect of antimicrobial effectiveness relative to the two preservatives individually in this formulation.

Description of the drawings

Figure 1 contains a flow diagram to clearly describe the manufacturing process involved to produce a formulation of the present invention.

Figure 2 contains a cross section description of a suitable container for the formulation of the present invention.

Figure 3 contains a cross section diagram of a pump system (Valois VP3/50) with actuator suitable for use in a container such as that described in Figure 2.

Figure 4 compares the effect of BANS, Aldecin™ AQ and a control upon TDI-induced nasal symptoms at differing time intervals from drug administration.

Figure 5 compares the effect of BANS, Aldecin™ AQ, a vehicle and a control upon antigen induced nasal vascular permeability at a suitable time from drug administration.

Figure 6 compares the effect of BANS, Aldecin™ AQ, a vehicle and a control upon the increase in intranasal pressure from 0 to 28 minutes after antigen challenge.

Figure 7 shows the results of the challenge test of BANS and the same formulation without one of each of the two preservatives against Ps. cepacia.

Abbreviations

BANS	beclomethasone dipropionate anhydrate aqueous nasal spray (following Example 1, except where indicated)
BDP	beclomethasone dipropionate
TDI	toluene 2,4-diisocyanate
FCA	Freund complete adjuvant
PCA	Passive cutaneous anaphylaxis
DNP-As	Ascari's suum extracts conjugated with dinitrophenol (antigen)
OVA	Ovalbumin (antigen)
BKC	Benzalkonium chloride
PEA	Phenylethyl alcohol

Throughout the specification and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

C L A I M S

1. A pharmaceutical formulation which comprises an aqueous solution of carboxy methylcellulose sodium, glycerol, propylene glycol and polyoxyethylene (20) sorbitan monooleate, containing suspended therein particulate microcrystalline cellulose and beclomethasone dipropionate anhydrate, characterised in that said aqueous suspension further comprises:

Dextrose;
Phenylethyl alcohol;
Benzalkonium chloride;
Disodium hydrogen orthophosphate; and
Citric acid.

2. A pharmaceutical formulation according to claim 1 characterised in that it is buffered to a pH of between 5 and 6.

3. A pharmaceutical formulation according to claim 1 characterised in that it is isotonic with fluids of the nasal cavity.

4. A pharmaceutical formulation according to claim 1 having a composition as follows:

Micronised beclomethasone dipropionate anhydrate	0.1% (w/w)
Dextrose anhydrous	5.0% (w/w)
Microcrystalline cellulose and carboxymethylcellulose sodium (Avicel RC591)	1.5% (w/w)
Phenylethyl alcohol	0.275% (v/w)
Benzalkonium chloride solution 50% (w/v)	0.04% (v/w)
Glycerol	4.0% (w/w)
Propylene glycol	1.0% (w/w)

Polyoxyethylene (20) sorbitan monooleate	0.007% (w/w)
Disodium hydrogen orthophosphate anhydrous	0.31% (w/w)
Citric acid monohydrate	0.2% (w/w)
Purified water	to 100%.

5. A container comprising a pharmaceutical formulation according to claim 1 suitable for delivering it in the form of a nasal spray.

6. A pharmaceutical formulation according to claim 1 for use in the treatment or prophylaxis of allergic rhinitis.

7. Use of a pharmaceutical formulation according to claim 1 in the manufacture of a medicament for the treatment or prophylaxis of allergic rhinitis.

8. A method of treatment of allergic rhinitis which comprises administering to a patient a pharmaceutically acceptable amount of a formulation according to claim 1.

9. A process for preparing a formulation according to claim 1 as herein before described by reference to the manufacturing flow diagram shown in Figure 1.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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WO 01/10409 A1

(54) Title: AQUEOUS NASAL FORMULATION

(57) Abstract: The present invention provides an aqueous nasal formulation comprising beclomethasone dipropionate anhydrate for use in the treatment of respiratory disorders.

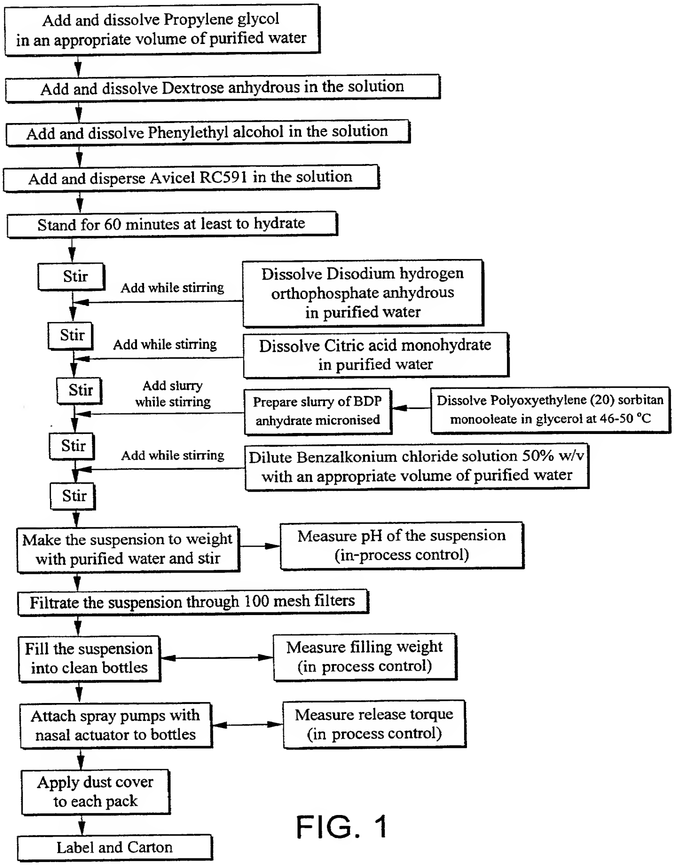

Add and dissolve Propylene glycol in an appropriate volume of purified water
Add and dissolve Dextrose anhydrous in the solution
Add and dissolve Phenylethyl alcohol in the solution
Add and disperse Avicel RC591 in the solution
Stand for 60 minutes at least to hydrate
Stir
Add while stirring
Dissolve Disodium hydrogen orthophosphate anhydrous in purified water
Stir
Add while stirring
Dissolve Citric acid monohydrate in purified water
Stir
Add slurry while stirring
Prepare slurry of BDP anhydrate micronised
Dissolve Polyoxyethylene (20) sorbitan monooleate in glycerol at 46-50 °C
Stir
Add while stirring
Dilute Benzalkonium chloride solution 50% w/v with an appropriate volume of purified water
Stir
Make the suspension to weight with purified water and stir
Measure pH of the suspension (in-process control)
Filtrate the suspension through 100 mesh filters
Fill the suspension into clean bottles
Measure filling weight (in process control)
Attach spray pumps with nasal actuator to bottles
Measure release torque (in process control)
Apply dust cover to each pack
Label and Carton

FIG. 1

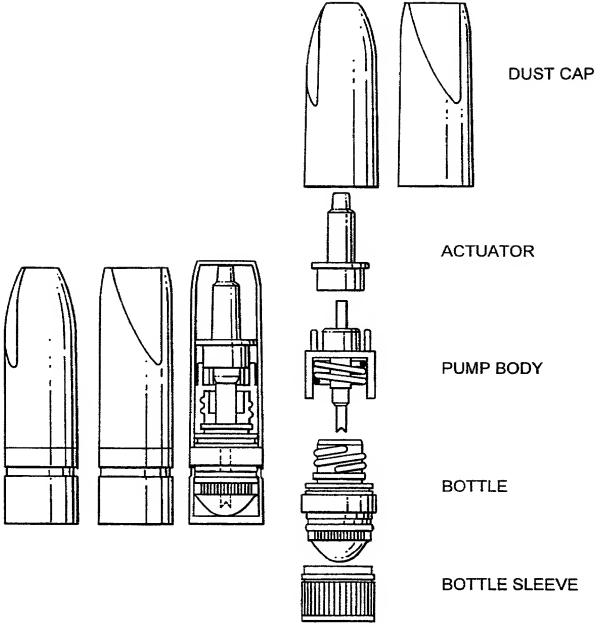


FIG. 2

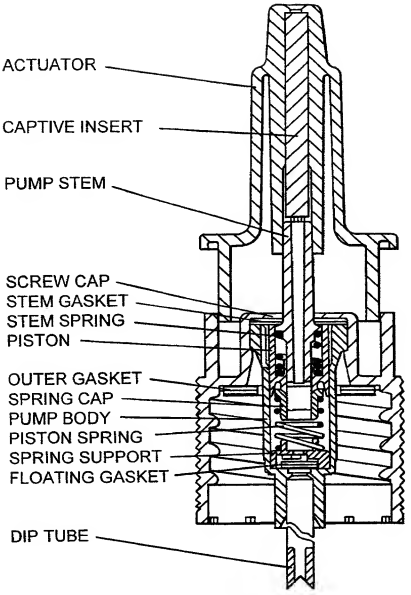


FIG. 3

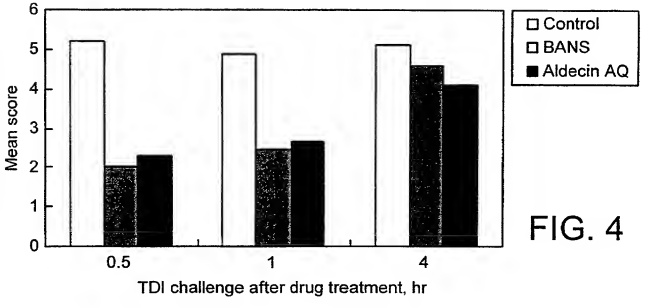
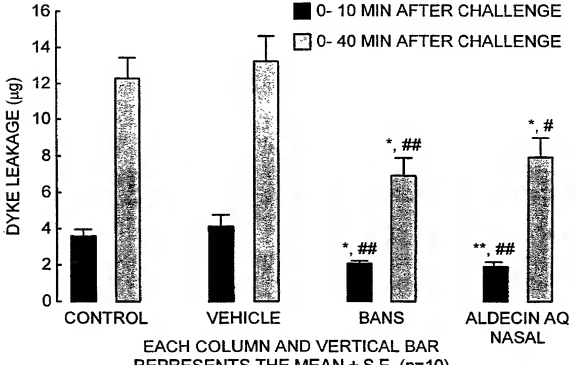
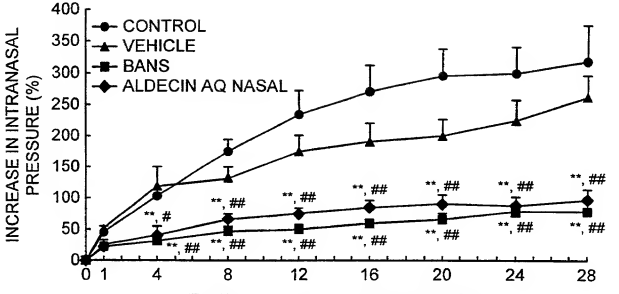


FIG. 4



EACH COLUMN AND VERTICAL BAR REPRESENTS THE MEAN ± S.E. (n=10)
*p<0.05, **p<0.01, VS CONTROL (TUKEY'S TEST)
#p<0.05, ##p<0.01, VS VEHICLE (TUKEY'S TEST)

FIG. 5



EACH POINT AND VERTICAL BAR REPRESENTS THE MEAN ± S.E. (n=10)
**p<0.01, VS CONTROL (TUKEY'S TEST)
#p<0.05, ##p<0.01, VS VEHICLE (TUKEY'S TEST)

FIG. 6

CHALLENGE TEST OF BANS AGAINST PS. CEPACIA

	LOG_{10} REDUCTION*				
	LOG_{10} INNOCULUM COUNT	2 DAYS	7 DAYS	14 DAYS	28 DAYS
BKC 0.02% w/w	6.2	0.3	1.0	1.3	1.8
PEA 0.275% v/w	6.2	0.2	0.6	1.7	NR
BKC 0.02% w/w + PEA 0.275% v/w	6.2	NR	NR	NR	NR

*: LOG_{10} REDUCTION = LOG_{10} (INNOCULUM COUNT) - LOG_{10} (SAMPLE COUNT)
NR: NO RECOVERY

FIG. 7

COMBINED DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY	ATTORNEY'S DOCKET **PJ3732USW**
	First Names Inventor: **Rika AKUTSU**
( ) Declaration submitted with initial filing or (x)Declaration submitted after initial filing (surcharge required 37CFR1.16(e))	***Complete if known:*** App No.:
	Filing Date
	Group Art Unit:

As below named inventor. I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

AQUEOUS NASAL FORMULATION

the specification of which (check only one item below):

[ ]is attached hereto.
OR
[x] was filed on <u>**3 August 2000**</u> as United States application Serial No. ____________ or **PCT** International

Application Number <u>**PCT/JP00/05200**</u> filed and was amended on (MM/DD/YYYY) ________________(if applicable)

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56.

I hereby claim foreign priority benefits under 35, U.S.C. §119 (a)-(d) or §365(b) of any foreign applications(s) for patent or inventor's certificate or 365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed:

PRIOR FOREIGN AND ANY PRIORITY CLAIMS UNDER 35 U.S.C. 119:

Prior Foreign Application Number (s)	Country	Foreign Filing Date (MM/DD/YYYY))	PRIORITY CLAIMED
1. 9918559.7	GB	08/07/1999	X
2.			
3.			

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional application(s) listed below:

Application No.	Filing Date (MM/DD/YYYY)	Priority Claimed
1.		
2.		
3.		
4.		
5.		

DECLARATION FOR "371" APPLICATION

COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued	ATTORNEY'S DOCKET NUMBER PJ3732USW

I hereby claim the benefit under 35, U.S.C. §120 of any United States application or §365(c) of any PCT international application designating the United States of America that is listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 C.F.R. §1.56 which became available between the filing date of the prior application(s) and the national or PCT international filing date of this application:

PRIOR U.S. PARENT APPLICATION or PCT PARENT APPLICATION

U.S. Parent Application or PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	STATUS (Check one) PATENTED	PENDING	ABANDONED

Send Correspondence to:	Direct Telephone Calls to:
23347 PATENT TRADEMARK OFFICE	James P. RIEK 919-483-8022

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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DECLARATION FOR "371" APPLICATION

COMBINED DECLARATION FOR UTILITY or DESIGN PATENT APPLICATION WITH POWER OF ATTORNEY Continued				ATTORNEY'S DOCKET NUMBER **PJ3732USW**
2	FULL NAME OF INVENTOR	FAMILY NAME **ONOZAKI** 5-d	FIRST GIVEN NAME **Tomohisa**	SECOND GIVEN NAME/INITIAL
	INVENTOR'S SIGNATURE	Signature x Tomohisa Onozaki		Date: x 7th May, 2002
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	INVENTOR'S SIGNATURE	Signature x Nobuya Sugibayashi		Date: x 7th May, 2002
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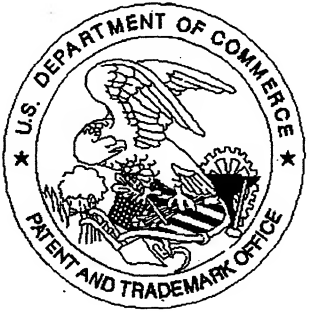

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